**PATENT**

**Attorney Docket No.: D5053-00031**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: **Anthony William Sly**

Examiner: **Zohreh A. Fay**

Serial No.: **10/781,179**

Group Art Unit: **1618**

Filed: **February 18, 2004**

Confirmation No.: **1823**

For: **OPHTHALMIC FLUID**

**CERTIFICATE OF MAILING, 37 C.F.R. §1.8(a)**
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Richard A. Paikoff
Richard A. Paikoff, Reg. No. 34,892
2/14/06
Date

## TRANSMITTAL LETTER

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_X_ Appeal Brief (submitted in triplicate).

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_X_ Other: Return postcard.

Respectfully submitted,

Date 2/14/06

Richard A. Paikoff

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PATENT Attorney Docket No.: D5053-00031

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Pursuant to 37 CFR §1.10, I hereby certify that this document is being deposited with the United States Postal Service on the date shown below to the following: Mail Stop Appeal Brief- Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Richard A. Paikoff

Richard A. Paikoff, Reg. No. 34,892

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF

Pursuant to 37 CFR §41.37, Appellant hereby submits this appeal brief. The appeal brief is being timely submitted under 37 CFR §41.37(a). The appeal brief is being submitted in triplicate.

Respectfully Submitted,

Richard A. Paikoff

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## TABLE OF CONTENTS

## I. Real Party in Interest

The real party in interest is Planned Products Pty Ltd., present owner of the application and the invention described therein.


## II. Related Appeals and Interferences

There are no related appeals or interferences.

## III. Status of Claims

Claims 7-11 are pending in the present application. Claims 7-11 stand rejected.

## IV. Status of Amendments

An after-final amendment was filed on October 17, 2005, but the amendment was refused entry in an Advisory Action dated November 30, 2005.

## V. Summary of Claimed Subject Matter

Appellant's invention relates to an ophthalmic product. Specifically, the invention relates to an ophthalmic fluid containing at least one triglyceride, diglyceride, or monoglyceride which is chemically similar or compatible with compounds found naturally in the lipid layer of the tear film of an ocular substrate. The glycerides are preferably derived from a fatty acid containing at least one unsaturated bond in a cis-configuration in the fatty acid residue. The ophthalmic fluid is arranged in use to provide a protective film: (1) across a tear film of an ocular substrate, and (2) intermediate a lipid layer of the tear film of the ocular substrate and a contact lens.

The tear film, which is the interface between the external environment and the ocular surface, has several different functions. It forms a smooth refractive surface over the otherwise irregular corneal surface, and lubricates the eyelids. Moreover, it maintains an optimal extracellular environment for epithelial cells of the cornea and conjunctiva where the electrolyte composition, osmolarity, pH, oxygen and carbon dioxide concentrations, nutrient and growth factor concentrations are regulated within narrow limits. 1:8-14 (References are to the application by page and line number).

Tears dilute and wash away noxious stimuli, provide an antibacterial system for the ocular surface and serve as an entry pathway for polymorphonuclear leukocytes in the case of

injury to the ocular surface. As tears have many different functions, it is not surprising that they have a complex structure and are produced by several different sources. 1:15-19.

The tear film consists of three layers:

(1) The inner layer is a mucous layer that coats the cornea and conjunctiva. It was previously thought to be 1 μm, but new evidence suggests that it may be far thicker;

(2) The mucous layer consists of mucins, electrolytes, water, IgA, enzymes, glycocalyx, microvilli, immunoglobins, and glycoproteins. The middle layer is an aqueous layer that is about 7 μm thick. This layer contains electrolytes, water, IgA, and proteins, many of which are antibacterial enzymes;

(3) The outer layer is a lipid layer about 0.1 μm thick, which floats on the aqueous layer. The lipid layer contains a complex mixture of hydrocarbons, squalene, wax esters, cholesterol esters, triglycerides, diglycerides, monoglycerides, free fatty acids, free cholesterol, phospholipids, sterol esters, and polar lipids. 1:20-29.

Each layer of the tear film is secreted by a different set of orbital glands. The lipid layer is secreted primarily by the meibomian glands located in the tarsal plates of the lower and upper lids. The glands lie in a row at the edge of the upper and lower eyelids, and their ducts open directly onto the inner margin of the eyelids. There are approximately 30 to 40 meibomian glands in the upper lid and 20 to 30 smaller glands in the lower lid. Each gland has an orifice that opens on the lid margin between the tarsal "grey line" and the mucocutaneous junction. The sebaceous glands of Zeis, located at the palpebral margin of the tarsus, and the aprocine glands of Moll, located at the roots of each eyelash, also secrete lipid that is incorporated into the tear film. 1:30-32; 2:1-7.

Sebum, also called meibum (the meibomian gland secretion), increases the surface tension of the tear film and decreases its rate of evaporation. The evaporation rate of the normal tear film is low because of the protective lipid layer. Approximately 10% - 20% (0.085 μL/minute) of the total tears secreted are lost by evaporation. In the absence of the protective lipid layer, the rate of evaporation is increased 10 to 20 times (1.7 μL/minute). 2:8-13.

Meibomian gland secretions contribute to the formation of a stable tear film, and its gland dysfunction may result in dry eye syndrome, keratoconjunctivitis and contact lens intolerance, presumably due to an inadequate or a compromised tear film, secondary to the meibomian gland dysfunction itself. Meibomian gland dysfunction may be often induced by soft contact lens wear, while mebomianitis may result from hard contact lens wear. 2:14-19.

There are two major types of dry eye syndromes: (1) Aqueous deficient dry eye syndrome is caused primarily from a lack of tear secretion from the lachrymal gland, whereas (2) evaporative dry eye syndrome is typically caused by lipid insufficiency, a condition related to meibomian gland dysfunction. Both syndromes often co-exist. 2:20-23.

It is thought that meibomian gland dysfunction may be caused in response to decreased androgen levels. Human lachrymal glands, meibomian glands and other ocular tissues have androgen receptors. The meibomian gland in particular appears to be a principal target site for androgen activity on the ocular substrate. Androgens appear to stimulate meibomian gland cells to produce lipids, which maintain tear film stability and prevent tear film evaporation. Decreased androgen levels frequently occur with fluctuating hormonal changes associated with menopause, pregnancy, lactation and through the use of oral contraceptives. It is also associated with the ageing process in men and women. Autoimmune diseases such as Sjörgen's syndrome, rheumatoid arthritis, diabetes, thyroid abnormality, asthma, cataracts, glaucoma and lupus appear to correlate with the presence of meibomian gland dysfunction and evaporative dry eye syndrome. 2:24-32; 3:1-3.

Certain medications such as antidepressants, decongestants, diuretics, ulcer medications, tranquillizers and beta blockers can also decrease the body's ability to produce lubricating lipids. The use of antiandrogen medications for prostatic hypertrophy or cancer also appears to correlate with the incidence of meibomian gland dysfunction and evaporative dry eye syndrome. Evaporative dry eye syndrome may also be caused by environmental conditions, such as exposure to smoke, fluorescent lights, air pollution, wind, heaters, air conditioning and dry climates. 3:4-12.

Contact lens wearers appear to be particularly susceptible to evaporative dry eye syndrome. Contemporary contact lenses are of two primary types: rigid gas permeable lenses

(hard) and hydrogel lenses (soft) comprising between 30% to over 85% water of hydration. Rigid gas permeable lenses are commonly formed from a co-polymer of methylmethacrylate and silicon, termed siloxaneacrylate. 3:15-19.

The tear film thickness on the eye is reported to be up to 10 microns, decreasing to 4.5 microns between blinks. The tear film is relatively thin when compared with the thickness of any contact lens, which varies from a minimum of 30 microns to an average of 60-120 microns, and over 250 microns for lenses of considerable optical power. Thus, the sheer mass of any contact lens may compromise the specific functions of the tear film, which include flushing action, prevention of desiccation of the ocular tissue, lubrication of the ocular and palpebral surfaces, formation of an optically smooth curved surface, a vehicle for oxygen and carbon dioxide transport, and defense of the cornea against trauma, infection or disease. The role of the lipid layer in preventing evaporation is relevant to contact lens wear. If the meibomian glands are obstructed, essentially eliminating the lipid layer, the rate of evaporation dramatically increases by a factor of 10 - 20. 3:20-31.

The lipid layer on the surface of all contact lenses is compromised as compared to the lipid layer of the cornea without contact lenses. A well-fitted contact lens has to rest on a continuous aqueous tear layer sandwiched between the lens and the epithelium, and it has to be coated with a continuous tear film complete with a superficial lipid layer. However, all contemporary contact lenses are unable to mimic the ocular surface properties, and therefore a comparable tear film on the lens surface is unable to form. 4:1-7.

A lipid layer does not form on hard lenses. There are conflicting reports regarding the presence and/or characteristics of the lipid layer forming on soft lenses, with some claiming the complete absence of a lipid layer, while others reporting it as present but thin, its depth being dependent on the water content of the lens. 4:8-11.

Clinical experience indicates that individuals without objective signs of dry eyes or related subjective symptoms may experience classical dry eye symptoms while wearing contact lenses. When the contact lens is placed on the eye, the lens alters the normal structure of the tear film and affects its rate of evaporation. It is thought that the lipid layer is compromised, causing dehydration of the aqueous layer to accelerate and tears to macerate the skin. 4:12-17.

## VI. Grounds of Rejection to be Reviewed on Appeal

Whether claims 7-11 are properly rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,981,607 to Ding et al.

## VII. Argument

### 1. Ding et al. does not teach or suggest Applicant's claimed invention.

Claims 7-11 were rejected under 35 U.S.C. §103(a) as being unpatentable over Ding et al., U.S. Patent No. 5,981,607. The Office Action of June 16, 2005 states, inter alia, that the reference differs from the claimed invention in the addition of fatty acids to a contact lens, and then placing the contact lens in the eye as a protective film, and that it would have been obvious to use a different means of administration for an ophthalmic product.

A *prima facie* case of obviousness under §103 exists only if the prior art reference(s) "teach or suggest all of the claim limitations" and there is "some suggestion or motivation . . . to modify the reference or to combine the reference teachings." MPEP 2142 (citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)). The Examiner has not established a *prima facie* case of obviousness because the reference does not to teach or suggest each feature of the claims and because there is no suggestion or motivation to modify the teachings of the cited reference, as argued below.

Ding et al. relates to an eye drop composition for alleviation of dry eye related symptoms in dry eye patients and contact lens wearers, which includes an emulsion of a higher fatty acid glyceride, polysorbate 80 and an emulsion stabilizing amount of Pemulen® in water, suitable for topical application to ocular tissue.

At column 3 lines 32-38 of Ding et al., it is stated that their invention is: *"directed to an emulsion system which utilizes higher fatty acid glycerides but in combination with polysorbate 80 which results in an emulsion with a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues as well as being suitable for alleviating dry eye symptoms."* There follows a statement of the invention which states that it is directed to a non–irritating pharmaceutical composition comprising an admixture of an emulsifying amount of a higher fatty acid glyceride and polysorbate 80. At column 4 lines 57-60 of the reference, it is noted that the discovery on which the invention of Ding et al. is founded: *"relates to an emulsion of a higher fatty acid glyceride such as, for example, castor oil, corn oil, sunflower oil or light mineral oil and an emulsifier and dispersing agent, polysorbate 80."*

The Ding et al. specification then goes on to discuss the composition of polysorbate 80, which is a mixture of oleate esters of sorbitol and sorbitol anhydrides condensed with approximately 20 moles of ethylene oxide. Furthermore, referring back to column 3 at line 54 onward, it is stated that the weight ratio of castor oil to polysorbate 80 is between about 0.3 to about 30. Thus, it is clear that the polysorbate 80 is a substantial component of the emulsion of Ding et al.

Please note that the ophthalmic fluid of the present invention is not an emulsion. In particular, it does not contain polysorbate 80 or any compound of a similar nature to polysorbate 80. In contrast to Ding et al., in the present invention as claimed, the ophthalmic fluid consists essentially of a glyceride. Furthermore, it is clear from the examples of Ding et al. that it is intended that the Ding et al. emulsion be applied directly to ocular tissue, so as to deliver a medication thereto. In fact, claim 1 of Ding et al. recites: *"A method for alleviation of dry eye related symptoms in dry eye patients and contact lens wearers, said method comprising topically applying to ocular tissue an emulsion of a higher fatty acid glyceride, polysorbate 80 and an emulsion stabilizing amount of Pemulen in water..."* In contrast, in the present invention the ophthalmic fluid is not applied directly to ocular tissue; the ophthalmic fluid is applied to an inner surface of a contact lens, as disclosed in the present specification at e.g., page 6, paragraph 1 and as presently claimed. Subsequently, the coated inside surface of the contact lens is applied to an ocular substrate.

**2. Appellant's Declaration under 37 CFR §1.132 demonstrates the non-obviousness of the claimed invention.**

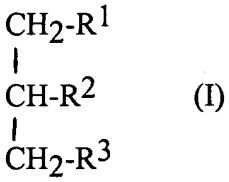
The above-described method of application in the present invention is significant, as is discussed in the previously submitted 37 CFR §1.132 Declaration by the inventor of the present application, which is attached herewith. This Declaration was presented with Appellant's Amendment and Response under 37 CFR §1.116(a), and was submitted under 37 CFR §1.116(e) in order to assist the Examiner in appreciating the distinctions between the present invention and the prior art, and also to simplify the issues for Appeal. As an aside, note that in the section titled *Affidavit or Other Evidence* on the Advisory Action mailed November 30, 2005, no indication was given that the Declaration would not be entered, i.e., the appropriate box to designate such was not checked. While this oversight is indeed minor, Appellant's reasons for introducing the Declaration with his Response to the Final Rejection retain their importance at Appeal as well: To simplify the issues related for Appeal, and assist the Examiner in appreciating the distinctions between the present invention and the prior art.

As explained in the Declaration by the inventor of the present application, in Ding et al., each droplet of triglyceride will be surrounded by adsorbed surfactants. This leads to repulsion between the droplets in the emulsion, preventing the droplets from spreading out into a uniform layer. Note that the present invention is directed to treating Contact Lens Intolerance (CLI), whereas Ding et al. is concerned with treatment of KCS (Kerato Conjunctivitis Sicca). Based on the discussion in the attached Declaration, a lipid monolayer cannot form in the presence of the surfactants polysorbate 80 and Pemulen®, and the disclosure of Ding et al. would be inoperative for purposes of the presently claimed invention. Therefore, there is no teaching, suggestion or motivation in Ding et al. to adopt the method of the present invention as claimed, and this rejection is overcome.

## VIII. CLAIMS APPENDIX

1-6 (cancelled).

7 (previously presented). A method of providing a protective film intermediate a lipid layer of a tear film of an ocular substrate and a contact lens, comprising topically applying to an inner surface of the contact lens a coat of an ophthalmic fluid and subsequently applying the coated inner surface of the contact lens to the ocular substrate, wherein the ophthalmic fluid consists essentially of at least one glyceride of formula (I):



(I)

wherein $R^1$=$R^2$ =$R^3$ is O-CO-R; or $R^1$=$R^3$ is O-CO-R when $R^2$ is OH; or $R^1$ is O-CO-R when $R^2$=$R^3$=OH; R is a fatty acid residue comprising 16-20 carbon atoms and containing at least one unsaturated bond, and R is the same or different when $R^1$=$R^3$ or $R^1$=$R^2$=$R^3$.

8 (original). The method according to Claim 7, characterized in that irritation to the ocular substrate associated with the application of the contact lens to the ocular substrate is reduced.

9 (original). The method according to Claim 7, characterized in that the method reinforces the lipid layer of the tear film of the ocular substrate upon application of the contact lens to the ocular substrate.

10 (original). The method according to Claim 7, characterized in that the fatty acid residue contains at least one unsaturated bond in a *cis*-configuration.

11 (previously presented). The method according to Claim 7, characterized in that the ophthalmic fluid contains at least one triglyceride, diglyceride, or monoglyceride derived from linoleic acid, linolenic acid, palmitoleic acid, arachidonic acid, or mixtures thereof.

12-15 (cancelled).

## IX. EVIDENCE APPENDIX

In this appeal, Appellant relies on evidence previously submitted pursuant to 37 CFR §1.132, attached herewith.

## X. RELATED PROCEEDINGS APPENDIX

As set forth above, there are no related appeals and interferences, and thus no decisions to be submitted.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | |
|---|---|---|
| Application No. | : | 10/781,179 |
| Applicant | : | Anthony William Sly |
| Filed | : | February 18, 2004 |
| TC/A.U. | : | 1614 |
| Title | : | Ophthalmic Fluid |
| Docket No. | : | 283702-14-1 (D5053-00031) |
| Customer No. | : | 08933 |

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Richard A. Paikoff
Richard A. Paikoff, Reg. No. 34,892
10/17/05
Date

## DECLARATION OF ANTHONY W. SLY PURSUANT TO 37 C.F.R. § 1.132

I hereby declare as follows:

1. I am the same Anthony W. Sly who is named as the inventor of the invention described and claimed in the patent application referenced above.

2. I have reviewed the Ding et al. reference, U.S. Patent No. 5,981,607 cited by the Examiner in the Office Action in the patent application referenced above.

3. Note that the present invention is directed to treating Contact Lens Intolerance (CLI), whereas Ding et. al. is concerned with treatment of KCS (Kerato Conjunctivitis Sicca).

4. As will be explained in more detail below, in Ding et. al., each droplet of triglyceride will be surrounded by adsorbed surfactants. This leads to repulsion between the droplets in the emulsion, preventing them spreading out into a uniform layer.

5. In KCS, the sufferer has difficulty producing a tear film, which leads to the dry eye symptoms as discussed in Ding et. al. However, with CLI, the sufferer has difficulty maintaining a uniform lipid layer over the tear film and the contact lens. If the lipid layer is compromised in any way the tear film evaporates much more quickly than is normal. The use of

the triglyceride layer in the present invention enhances the protection normally provided by the lipid layer.

6. A monolayer of triglycerides is formed by the effective bonding between the polar hydrophilic triglyceride head and nonpolar hydrophobic tail. In their pure state, the triglycerides adhere to each other in cohesive micelles. As concentration increases, lipid micelles (a) become crowded together, and coalesce into extended rods (b), then hexagonal aggregates of such rods (c), and finally into an aggregation pattern of significance - the bilayers (d). Like micelles, these are stabilized partly by internal van der Waals bonding between adjacent hydrocarbon tails and partly by polar interactions.

7. As disclosed in Ding et al., the combination of polysorbate 80 (surfactant) and Pemulen® (emulsion thickening agent), followed by agitation, generate short range repulsions, which help to stabilize emulsion droplets. On forming oil/water emulsions, Pemulen molecules form an adsorbed gel layer around each droplet, with the hydrophobic portions of the polymer anchored in the oil phase. Thus, when two oil droplets approach each other, a physical repulsive force is generated by the presence of these adsorbed layers.

8. If the oil droplets or the substrate are covered by a surfactant, as in emulsion systems, surfactant molecules from the continuous phase can be adsorbed into the substrate. Consequently, the droplet does not spread on the substrate if surfactant layers repel each other. This is why oil droplets stabilized in water by traditional surfactants do not spread on hydrophobic substrates. The surfactant encapsulated oil micelle also has relevance when considering the resident tear film lipid layer of the Kerato Conjunctivitis Sicca (KCS) sufferer, where free surfactant molecules are adsorbed by the tear film lipids and the contact lens matrix, thereby decreasing the lipid integrity adhesion and cohesion stability, disenabling the required

smooth refractive surface, and ultimately increasing dehydration of the lens and evaporation of the aqueous phase of the tear film.

9. Therefore, based on the above discussion, a lipid monolayer cannot form in the presence of the surfactants polysorbate 80 and Pemulen, and the teachings of Ding et al. would be inoperative for purposes of the presently claimed invention.

10. I have recognized Contact Lens Intolerance (CLI) as a condition resulting from the typical application of a contact lens onto the eye surface which manifests as ocular irritation, tear film disruption, discomfort and onset dry eye symptoms. In the present invention, the application of neat triglycerides superficially to the contact lens provides a barrier of hydrophobic integrity of the lipids, creating a semi-permeable membrane intermediate the corneal surface and the contact lens. This prevents aqueous migration between the tear film and the contact lens, and the external environment. Also, contact between the lens and the eye surface is prevented, thereby obviating foreign body irritation. Ultimately, contact lens tolerance, comfort and long term experience are improved. The light passage through the lens to the retina is unaffected as the lipid layer maintains a smooth reflective surface which does not affect the lens quality. In KCS, there is a deficiency in aqueous tear secretion, so that the tear film does not cover the corneal surface evenly. Traditionally, if the lipid phase becomes reduced, evaporation of the precorneal tear film will increase. However, the lipid phase is not reduced in KCS. In CLI the subject shows a degraded lipid integrity, and normal lacrimal activity.

11. An important aspect of the present invention is the orientation of the monolayer in relation to the surface of the contact lens, as the fluid itself has a non-polar hydrophobic tail and a polar head. Lipid integrity in the formula is needed to create and maintain

a stable and cohesive membrane and adhesion to the contact lens. The contact lens itself is of high porosity, with a negatively charged surface. The polarity has an important role in the understanding of the positioning of the monolayer matrix in relation to the contact lens surface, as the formation of the monolayer superficial to the contact lens surface fulfills the following functions: (1) forming a malleable barrier between the lens membrane and the epithelium of the eye; (2) reducing protein adsorption of the lens by intercepting the proteins; and (3) providing osmotic interference via a semi-permeable membrane.

12. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent application or any patent issuing thereon.

11 October 2005 By: _____
Date Anthony W. Sly